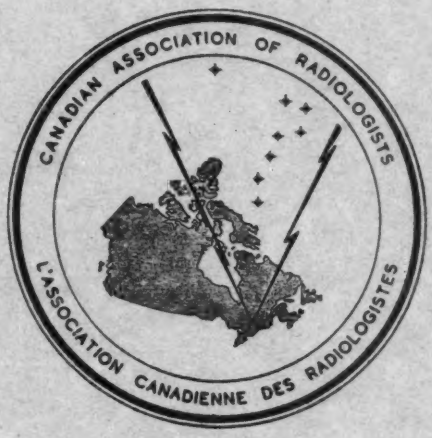
Journal of the Canadian Association of Radiologists



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THE KNOWN AND POTENTIAL VALUE OF RADIOACTIVE ISOTOPES AS THERAPEUTIC AGENTS

Gordon E. Richards Memorial Lecture,
Canadian Association of Radiologists,
Quebec, 14th January, 1954

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Montreal

Your invitation to give the second Gordon E. Richards Memorial Lecture has bestowed upon me a very great honour, of which I am deeply conscious and most appreciative.

Cet honneur m'est d'autant plus sensible que la réunion de notre société à Québec est pour moi un anniversaire de votre accueil très aimable alors que j'étais relativement un étranger. A cette occasion-là, j'eus surtout conscience de la gracieuse réception par Gordon Richards et mes confrères de langue française. Depuis ce temps-là, au fur et à mesure que les années passaient, l'une des expériences les plus savoureuses dans ma vie a été le développement des amitiés dont vous m'honorez.

My first acquaintance with Gordon Richards was about twenty-five years ago, when we were introduced by my "chief", Dr. Preston M. Hickey. I met him subsequently at meetings, from time to time with other Canadian "greats" in Radiology, of whom some of you will remember Dr. A. H. ("Sandy") Pirie, Dr. Herbert McGuffin and Dr. Leo Pariseau. But it was not until some years later that my growing regard for his thoughtful approach to the many problems in radiation therapy was to have the fortunate opportunity to develop into a warm and close friendship, within which I was admitted to his innermost professional thought and struggle towards an ideal. There were times when he was beset by professional hurts and rebuffs, which he bore without rancour. His devotion to his patients, his constant concern for the unfortunate person with cancer, his continuing search for a better way to effect adequate treatment in order to control if not cure their malady, (as indicated by 28 of his 41 scientific papers, many of them classics), his interest and insistence upon as good a training as possible in radiologic techniques and diagnosis for young medical officers of the armed forces, the education of the medical student and the post-graduate, the establishment of proper standards for qualification of specialists in his chosen field, the recognition of Radiology by the Royal College of Physicians and Surgeons, the inauguration and development of the Ontario Cancer Foundation, — all these were but a few of the many facets of Gordon Richards' professional life, by which the Canadian scene, and in a very real measure the field of radiation therapy internationally, was enriched by him.

Those of us who were also privileged to know something of the man personally will remember for a long time the severity with which he criticized his own work, his deep concern for the best interests of his three sons and his great sorrow in the loss of one during the war.

The subject which I have chosen to discuss was the topic of several conversations I had with Dr. Richards, before and during our work together in the Section on Radiology of the Sub-committee on Surgery in the Medical Division of the National Research Council, and, later, on the Advisory Committee of the Atomic Energy Project. In fact, one purpose of my trip to Toronto on that unhappy day on which he had his first tell-tale haemogram, was to discuss some problems relative to isotopes. It seems fitting that together we critically survey here, much as he would have done had he been permitted to live, our present knowledge of radioactive isotopes as therapeutic agents and perhaps, their foreseeable potentialities.

It is appropriate also at this time as Radiologists of Canada assembled in Quebec Province, to pay homage to one of the "greats"

in the history of atomic physics, Ernest, Lord Rutherford, whose research at McGill University opened the door to our present-day relative familiarity with alpha and beta radiation. This year marks the fiftieth anniversary of the publication of Rutherford's book on the knowledge then available of "Radioactivity". I have no doubt that were he living in Canada today, we would be honoured by his active participation in our meetings. Further, as we today nonchalantly speak of a "Geiger counter", few realize that this useful instrument was developed under Rutherford's guidance by one of his pupils, Geiger by name.

Any consideration of radioactive isotopes as therapeutic agents, at the present time, is limited by the current factual evidence of their practical usefulness, certain clinical research into other applications, and some philosophic exploration of their potentialities so far as they may be projected within the limitations of our knowledge of normal and pathologic physiology as well as related nuclear physics.

The characteristics of each active isotope must be assessed primarily in regard to the purpose for which it is to be used; either as

(1) a substitute for an agent already available, but less plentiful, less versatile, less powerful, with greater possible side-effects or hazard, or some less favourable combination of these; or
(2) as a means to do a new job, such as by virtue of selective specific physiologic affinity for or by a specific organ or tissue.

It is evident at once that criteria of

(a) biochemical or pharmacologic suitability will be of prime importance in intracavitary, parenteral or interstitial administration; and
(b) physical characteristics must be considered in each instance.
Chemical and physical hazards in handing, as well as in possible accidents affecting personnel must be explored and reduced to a minimum.

Of the known and reasonably probable 1052 isotopes and isomeric pairs, 282 are stable; 118 have a half-life measured in seconds, 199 in minutes; and 96 decay 50% in less than 12 hours. If we subtract these and the 49 naturally radioactive elements and their isotopes, there remain some 209 unstable isotopes with half-lives ranging from twelve hours to sixty days, and 99 whose half-lives extend from two months to over 1000 years. The isotopes with half-lives less than 12-14 hours are relatively impratical for use therapeutically; those of greater than 30-40 days are probably not safe for parenteral administration.

The 70-odd possibly useful radioactive isotopes will have to be studied extensively before adequate assessment can be made of their therapeutic value. So far, only a few have been shown to be producible with present facilities in practical quantities, to possess suitable and useful physical characteristics, to be pharmacologically safe and physiologically effective.

The physical value of the radioactive isotopes will depend upon their relative emission of alpha, beta or gamma radiation, the energy and half-life of that radiation and the specific activity which can be induced in each, within practical limits.

With these generalizations, we may proceed to consideration of our present knowledge of the usefulness of various radioactive isotopes for irradiation therapy,

(1) Externally
(2) Interstitially
(3) Intracavitary
(4) Parenterally for systemic effect, or
(5) Parenterally for specific organic or specific cytologic effect.

The selection of a radioactive isotope for external, interstitial or intracavitary therapeutic irradiation in large measure will be as a substitute for the naturally radioactive elements (radium and radon) or x-radiation, with which we have become increasingly familiar for over fifty years. The essential criteria will be availability, facility of manipulation and of the superiority of its radiation in the induction of a more satisfactory biologic reaction because:

(a) the virtual total absorption by the superficial millimeters of tissue, as in the case of beta-emission, compares favourably for the purpose with that of low or medium voltage x-radiation; or
(b) its high-energy-level gamma emission, short wave-length and relatively monochromatic character will afford superior depth-doses as compared with high voltage x-radiation or large quantities of radium.

1. External Irradiation

Phosphorus^{32} and Cobalt^{60} are so far the major examples of the two contrasting requirements for external irradiation.

The beta-radiation of *Phosphorus*^{32} (half-life 14.3 days), whose particles have a maximum energy of 1.7 mev. (average 0.685 mev.), can penetrate tissue 7 — 8 mm., (average of 2.4 mm.). Low-Beer's (1950) blotting paper method, and the impregnated bakelite suggested by Raper and Barnes, and Bizzell and his associates (1951), has been improved upon by Walton (1950), Sinclair and Blondal (1952) in the impregnation of polythene plastic with red phosphorus (20% by weight), producing an easily handled thin sheet (55-65 mgm/cm^2) which, upon irradiation in a pile for about two weeks, can be brought to a specific surface intensity of 1500—2000 "r"/hr. Such an appli-

cator has a maximum inhomogeneity of 5%, and will afford a depth dose of 40% at 1 mm., 15% at 2 mm. If cemented to a lead-impregnated rubber backing, approximately 98% of the beta radiation from the outer surface will be absorbed. The surface contamination is minimal and can be removed readily with an alcohol sponge. This affords an excellent agent for the irradiation of thin superficial skin malignancies and pre-cancerous keratoses. The dose requirement is of the order of 7000 "r" (equivalent) for epidermolysis. Low-Beer has observed some excess regrowth and coarseness of hair following the initial epilation.

Strontium^{90}, also emitting a pure β-radiation of 0.65 mev, with a half-life of 25 years, has been developed in a surface applicator by Friedell and Thomas for the treatment of benign hypervascularization of the conjunctiva and cornea. This is an improvement over the older radium D E applicator.

Haybittle has recently (1953) described a new *Cerium*^{144} applicator, using silver foil (105 mgm/cm^2) in the place of the gold (50 mgm/cm^2) filter previously studied by Freundlich (1949), and a cone-collimator of perspex coated with 0.5 mm. lead foil. This is an interesting example of development of an applicator after special study of the physical characteristics of the source material. Cerium^{144} (half-life 282 $\pm$ 3 days) decays to Praeseodymium^{144} with a beta-emission of 0.3 mev. (70%) and 0.17 mev. Pr^{144} in turn, (half-life 17.5 minutes) with a beta-emission of almost pure 2.97 mev. and a small gamma component becomes Neodymium^{144}. The source material of 14.5 mc. of Ce^{144} Cl, evaporated over an area of 3 cms diameter, is sealed between the silver foils and so mounted in duraluminum, (as a holder as well as to minimize bremssstrahlung), as to be recessed 1.2 cm. from the skin surface. The dose rate at the centre of the applicator face is 59 "r"/min. with a half-value depth of approximately 250 mgm/cm^2. With addition of the collimator, which increases the source-skin distance to 3.4 cm., the half-value depth becomes approximately 325 mgm./cm^2. Using sheet celluloid to determine the half-value depth, he reports comparative figures of 100 mgm/cm^2 for a 20 mgm. Radium plaque (0.5 mm. monel face), approximately 90 mgm/cm^2 for Freidell's Strontium^{90} applicator and 60 mgm/cm^2 for a 3 cm. diameter Phosphorus^{32} (in plastic) source.

Ruthenium^{106} (half-life 1 year), 68% of whose radiation is β of 3.53 mev., has also been studied by Freundlich and by Krohmer. The latter has reported a half-value depth of 155 mgm/cm^2 for Ru^{106} with an aluminum filter of 67 mgm/cm^2 thickness.

Cobalt^{60} has been considered for the development of surface applicators to replace the radium plaques which have been a familiar part of our older facilities. However, much of the advantage of the radium plaque has been its beta-radiation, which Cobalt^{60} will not afford when encased in a necessary sheath. At present, no other element presents adequate qualities for practical use in this way.

For *teletherapy*, an isotope is required which will emit hard gamma rays, has a relatively long half-life, can be produced readily in considerable quantity and with adequate specific activity, possesses chemical and physical properties which make it convenient to work and to use, and can be procured at a relatively lower cost than radium.

Cobalt^{60}, with high energy gamma radiation of 1.169 and 1.331 (average 1.25) mev. and half-life of 5.3 years, has much to offer in the place of either radium or x-radiation at 2 — 3 million volts. The basic Cobalt^{59} is quite plentiful. Oxidation is slow. Although pure cobalt metal is hard and brittle, hence in preparation for interstitial use an alloy has been found advisable, it can be machined. Activation in the nuclear reactors is not difficult. Its magnetic properties make it quite readily handled by remote control, for packaging.

At the present time, it is more practical to consider than either Europium$^{152,\ 154}$ or Cesium^{137}. Cobalt^{60} has a markedly lower self-absorption factor than radium. Its roentgen equivalency is of the order of 1.356 rhm. per curie compared with 0.84 rhm. per gram of radium filtered by 0.5 mm. platinum.

In 1946, a specific activity of less than one curie per gram was optimistically anticipated. Today, 35 curies per gram is a standard for teletherapy unit sources, and a level of 60 — 70 curies/gram is within practical possibilities. Such a source, in the form of pellets can be produced with relative ease in a nuclear reactor with high flux. A capsule of such pellets, 2 cm. in diameter and volume of 9 cc at 35 C/gram will constitute an active source with a total energy level of approximately 1500 curies, and in a properly designed apparatus will deliver a well defined beam of 40 "r"/min. at 80 cms. source-skin distance.

The isodose pattern of such a beam is highly satisfactory, with a percentage depth dose of 50.7 to 56.6 at 10 cm. for field portals of 5 x 5 cm. to 10 x 12 cm., and of 22.8 to 28.1 over a similar range of fields at 20 cms. depth (Johns). The depth dose curve of Cobalt^{60} (Johns) lies approximately midway between those of 2 million volt x-radiation with a filter of 6 mm. Pb, 5 mm. Cu. and of 3 million volt x-radiation with a filter of 10 mm. Pb, 5 mm. Cu. as determined by Trumpp and Cloud.

This is not a cure-all, however, as some would believe, but unfortunately has so captivated the imagination of some public-spirited persons that there may be a rash of cobalt beam units in the near future. It is my opinion that Cobalt^{60} Beam Therapy facilities should be restricted to only those therapeutic centres which already are well-equipped with the older conventional radiation therapeutic apparatus, have some three hundred new cases of major malignant neoplasms per year to afford a sufficient number of patients for selection, are part of a relatively large general hospital with able consultants in all other fields of medicine, and are suitably staffed by experienced radiation therapists who personally direct the treatment, observe their patients daily and are familiar with the hazards of high exit-doses and variation of skin reaction from high energy sources compared to 200 — 280 kv x-radiation, and who also have associated with them competent radiation physicists. Although Watson and Johns have demonstrated the practical value of Cobalt^{60} Beam Therapy, its employment still remains in the field of clinical research.

Further, it must be kept in mind that the activity of these sources will diminish by slightly less than 50% in five years, requiring replacement if selective efficiency is to be maintained. Current dosage schedules will require periodic correction due to the normal decay.

The remainder of the gamma-emitting isotopes with sufficiently long half-life to be considered are not producable in sufficient quantity at present.

2. Interstitial Irradiation

Interstitial Irradiation with radioactive isotopes includes both

(a) the employment of solid applicators made of the active elements in the form of suture-like wires or threads, "grains" or "seeds" or needles; and

(b) the infiltration of the tissues directly with colloidal suspensions or solutions of the active elements. A number of factors must be considered.

(1) *Needles, sutures, et cetera.* Care must be taken in regard to the solid applicators that either the material is inert physiologically from the chemical standpoint or is so protected by some cover as to prevent absorption. Further, if the alpha or beta radiation is not desired, the sheathing must be designed to effect adequate filtration.

Cobalt^{60} is absorbable by body fluids, with toxic effect on the central nervous system and intestines, and in the pure state is quite brittle. Myers recommends an alloy, "cobanic" of 45% cobalt, 55% nickel. The radio-nickel produced during exposure in the pile is considered not to affect the total radioactivity significantly.

(Ni.^{59} has a beta emission of 0.67 mev., half-life 36 hours.)

As with Radium (Radium C-beta radiation maximum 3.15 mev.), an absorbing sheath must be used, for the beta radiation of Cobalt^{60} has a maximum energy of 0.308 mev., (mean energy of about 0.1 mev.,) with a maximum range of 80 mgm cm^2 in aluminum.

(The figure of 80 - 85 mgm cm^2 is not directly comparable for Radium C. It is probable that a density of 1,600 mgm cm^2 would be required to absorb *all* of its beta radiation, with maximum energy level of 3.15 mev. Platinum 0.5 mm. as normally used has a density of 1,072 mgm cm^2.)

Electroplating or sheathing of the cobalt with a thickness of 0.11 mm. nickel or silver, or 0.05 mm. gold could effect adequate filtration. This would permit introduction of the protected Cobalt^{60} into the tissues, provided the activity of such a sheath, induced during irradiation in the pile after its application to the "cold" wire, is within the limits of safety for the operator as well as the recipient, as to both its induced specific activity and its secondary radiation.

Gold or steel appear preferable. The maximum activity of Gold^{198} developed in a 3 cm. length upon irradiation of one month at a flux of 5 x 10^{11} neutrons cm^2 sec. would be 42 mc. This would decay in one month to some 19.2 microcuries, and to 6.6 millimicrocuries in a two month period of "cooling off". The Iron^{59} of a similar steel sheath would have comparable levels of 0.75 microcuries on irradiation, with a decay to 3.1 millimicrocuries in one year. The secondary radiation from a steel-sheathed source of Co^{60} has been determined by Japha as 35 microcuries millicurie.

The decay constant amounting to 1.08% per month (12.26% year) must be recognized, as in the Cobalt Beam unit, and dosage-time tables adjusted at least each six months.

Translation for comparison with dosage schedules in equivalent milligram-hours of Radium may be accomplished by using the specific dose rates, namely 13.5 (Co^{60}) 8.4 (Ra) = 1.607.

Physically, the dose distribution about linear Cobalt^{60} sources is comparable to Radium, with some differences due to the dimensions and physical characteristics of the active source. Sinclair states rather categorically that there is no significant difference in dosimetry, nor of biologic effect in

interstitial techniques with gamma emitters of energies from 0.3 mev. to 3.0 mev., provided the beta-emission is properly screened.

Meschan and associates believe they have observed a more intensive biologic reaction of the order of 15% from Cobalt^{60} sheathed in hyperchrome steel (wall thickness of 0.3 mm.), than from equivalent radium doses. Japha has reported on stainless steel sheathing (wall thickness 0.3 mm.). Wilson recommends a sheath of 0.5 mm. Pt. with which he finds 1 mc Co^{60} delivers 12.22 "r" equiv./hour.

Morton, Myer and Callendine advocate nylon tubing (0.25 mm. wall thickness), which they consider will absorb some 93% of the beta-radiation, as a conveyance for the Cobalt^{60}. The linear specific activity in all these approximates one millicurie centimeter. The use of aluminum spacers advocated by Myer, *et al.* permits considerable versatility in dose intensity.

Tantalum^{182} (half-life 111 days, beta-radiation 0.5 mev. maximum, gamma 1.13 mev.) has been advocated by Sinclair. It is physiologically inert, but requires screening of the beta-emission. In wire form, 0.2 mm. diameter, sheathed with 0.1 mm. Platinum, making a total diameter of 0.4 mm., it will afford an active source of approximately 0.9 mc/cm., delivering 6.12 "r"/hr./mc. at 1 cm. Lederman has used it satisfactorily in retinoblastoma. A heavier wire, approximately twice the diameter is better for tumours of the tongue and palate. Such a size would shorten the treatment time by a factor of 4, the activity per unit mass being comparable. Wallace and Stapleton have found such a source suitable for carcinoma of the bladder, administering a dose of 7000 "r" equivalent in 5 - 7 days with their "hair-pin" implants (0.8 mc/cm).

Gold^{198} (half-life 2.72 days, beta 0.96, 0.60; gamma 0.41, 0.16) in the form of "grains" can be used in lieu of radon gold seeds. With platinum as a beta filter, the dose at 400 mgm/cm^2 is 80%, compared with 75% for radon. On this continent the active gold wire is sheathed in inactive gold tubing. Holt, Sinclair and Smithers have developed a "gun" for making such implantations. This would afford multiple point sources and permit the therapist to effect a very even distribution. The short life of Au^{198}, however, requires close proximity in time to a thermal neutron reactor for practical use.

(2) *Interstitial infiltration* has been investigated by Kerr, Flocks, Elkins and Culp, using a colloidal suspension of Gold^{198}. A variable amount of fluid, usually between 8 and 16 cc. containing the active colloid, is injected within the capsule of the prostate and also peri-prostaticly, with a dose ratio of 2 millicuries per gram for the prostate and 5 - 10 millicuries to each seminal vesicle. An appreciable local beneficial result has been obtained at least temporarily in a high majority of cases. Some difficulty has been experienced with local reactions in the rectum. It is too early to fully assess the potential value of this method.

Some studies of the effect of parametrial injection of colloidal Gold^{198} have been made in monkeys by Nolan, Jones and Neil. The size of the colloid particles will affect the extent to which the active source may be carried along the lymph drainage bed and be able thereby to irradiate disseminated neoplasm. This also is still in the experimental stage, but opens a window on some possible vista for the future.

3. Intra-cavitary

Intra-cavitary application of the radioisotopes may be accomplished with solid units, or by means of fluids containing the active source in solution or colloidal suspension.

(a) A *solid source* may be in the form of beads or pellets for a cavity such as the maxillary sinus, in rods or wires as direct applicators after the Stockholm method for carcinoma of the cervix or corpus uteri, or inserted in applicators of the Ernst type. For these, virtually the same criteria pertain as in the case of interstitial use. The most satisfactory source to date, Cobalt^{60}, must be enclosed in some sheath metal to confine its tendency to flake, protect its brittleness, and also to screen its beta-radiation as a hazard to personnel as well as to the patient. The dosage calculations, selection of cases and reaction to be expected are essentially the same as for radium or radon, with due consideration for the physical variation in specific activity.

Another method for intracavitary use of a solid source has been devised by Cones and Gregory for the treatment of diffuse carcinoma of the urinary bladder. Cobalt^{60} sources in 0.5 mm. silver, composed of 2 x 2 mm. cylinders with total activity of either 23 mc. or 46 mc. are enclosed in a plastic capsule mounted on a nickel rod, which is in turn surrounded by a fabric-base latex catheter and and balloon. The latex catheter contains the necessary tubes for inflation of the balloon and for urinary drainage from the bladder. The balloons are of 5, 6 or 7 cms. diameter to permit selection of a size suitable to the patient.

After insertion of the instrument and proper adjustment to the patient, the balloon is distended with 5% NaI plus 0.5% $NaHCO_2$ coloured with green vegetable dye as an indicator in the urine if leakage occurs. This sus-

pends the active source in the centre of the bladder, and makes use of the spherical isodose surface of such cylinders at radii greater than 2 cms. The self-absorption of Co^{60} is less than 4%. The 23 mc. source delivers 23 "r"/hr., the 46 mc. unit 92 "r"/hr. The depth dose to the bladder wall (100% at the mucosal surface) at a

		depth	
radius of	0.5 cm.	1.0 cm.	1.5 cm.
2.5 cm. =	68%	50%	36%
3.0 cm. =	72%	53%	40%
3.5 cm. =	77%	60%	50%

The dose requirement in their experience is of the order of 6,500 - 7,000 "r" equivalent.

(b) The *fluid methods* include the use of solutions or suspensions of active sources either in a confining container or in a free space.

(1) *Hollow viscus:*

An example of the confining container is the counterpart of the suspended solid source just described for the urinary bladder. Müller (1949) proposed the application of a solution of Co^{60} in a balloon in the urinary bladder. Wallace (1949), and Walton and Sinclair (1952) used solutions of sodium^{24} chloride (Na^{24}, half-life 14.8 hours, β 1.4 mev., and γ 2.76, 1.38), or of Bromine^{82} (half-life 35 hours, β 0.46 mev., and γ 1.35, 0.79, 0.55) as calcium bromide, in a 150 ml. balloon.

In their experience, three serial fractionated doses of 200 β "r" + 500 γ "r" each, at weekly intervals, were more satisfactory than a single dose of 3,000 β "r" + 4,000 γ "r" with Na^{24}, or 4,000 β "r" plus 1,000 γ "r" with Br^{82}.

In the female, the balloon may be introduced per urethram; in the male via a small incision in the perineum and the posterior urethra.

Rather satisfactory results were obtained in selected cases of carcinoma of the urinary bladder which do not extend deeper than the sub-mucosa.

However, especially in the use of solutions of Co^{60} and generally in the other methods described, there are very definite technical difficulties in the proper introduction of such sources, together with real hazards to both patient and operator from exposure, leakage and contamination. Further, with either Sodium^{24} or Bromine^{82}, a short distance factor between the reactor pile and the recipient is essential, because of the short half-life of each.

(2) *Serous cavity* (pleura or peritoneum):

The direct application of radioactive isotope therapy to either the pleura or peritoneum requires serious consideration of the physiologic and pharmacologic characteristics of the medium and of the active material, as well as the physical activity of the isotope. In general, the medium must be non-irritating and non-toxic, and sufficiently stable to prevent uneven deposition of the active material. The colloidal particles must be of sufficient size (not less than 0.003 micron in diameter) so that they will not carry the active element into the blood or lymph stream for dissemination.

The active isotope should be available in relatively high specific activity so that large volume is not required, with a half-life sufficiently short to effect delivery of an adequate dose in a reasonably short time, a predominantly beta radiation for local effect upon the serous membranes and superficial implants, but with sufficient gamma component to permit external detection and assessment of the distribution.

The serous cavity itself must be relatively free of loculation and contain sufficient effusion to aid in wide dispersion of the injected material throughout the space. Estimates vary as to tissue dose.

Modification and retardation of embarrassing serous effusions, in those patients with pleural or peritoneal involvement due to disseminated metastatic neoplasm, (chiefly from the breast or the ovary), has been accomplished with colloidal Gold^{198} or colloidal Chromic Phosphate^{32}. Neither of these agents can be expected to affect large masses of the metastatic neoplasm, for the particles are purposely large enough to prevent passage into the lymph or blood stream. The reports on both indicate that an appreciable amelioration may be achieved. We have not had signal success in the few cases of gross sero-sanguinous pleural effusion or ascites so treated in the last stages of carcinoma.

Recently we have used Colloidal Gold^{198} for part of the primary active treatment of two patients with bronchogenic carcinoma. Following pneumonectomy, in a young man with a rapidly growing immature-cell type neoplasm, this was employed as a means to attack such free or superficially implanted cells as might be present, and enhance the external radiation effect. In the other man, of middle age, shortly following thoracotomy, who had a minimal sero-sanguinous pleural effusion presumably associated with the known multiple small pleural implants from an inoperable primary lesion, the philosophy was similar, — for the purpose of affecting the superficial lesions of the pleura and to enhance the effect of his external x-radiation therapy. So far, although only some three months in one, and less than two months in the other, all goes well.

Where the source of supply distance-time factor is important, the short half-life of Au^{198} has caused the search for some other element. Chromic phosphate appears to be the answer to some of the problem, affording a half-life of 14.3 days and the pure beta radiation (1.7 mev.) of P^{32}.

Chlorine[38] and Krypton[87] have been investigated for similar intraperitoneal and intrapleural use. But the half-life of Cl^{38} is only 37 minutes and of Kr^{87}, 74 minutes, which render them relatively useless generally.

Some may not agree that the *intra-bronchial insufflation* of Gold[198] can be included in the intra-cavitary group rather than parenteral.

Hahn and others have found that colloidal Au^{198} introduced into the bronchial tree of dogs was not picked up by the bronchial lymphatics in sufficient concentration under 15 days.

Müller and Rossier (1951), using microembolic technique via cardiac catheterization with gold adsorbed on carbon particles, observed a uniform irradiation of the capillary bed but no pick-up by the lymphatics.

Hahn, Corothers, et al., insufflating radioactive silver (Ag^{111}, half-life 7.5 days, beta radiation 1.0 mev.) colloid into the bronchi, noted rapid drainage into the regional lymphatics in 2 - 5 days.

Recently, using Gold [198] colloid of very high specific activity, developed with the high neutron flux available at Brookhaven, Hahn, Hilliard and Corothers have seeded a solution of Ag NO_3, then reduced the silver to metallic form with cevitamic acid. The resultant radioactive gold nuclei, coated with nonactive silver, were injected by bronchoscope under pontocaine anaesthesia into one of the non-affected lobes of a diseased lung in a dose of 0.5 ml./kgm (5ml = 15 mc Au^{198}) of body weight. At lobectomy 2 weeks later, it was found that the colloid had been drained off by the lymphatics. They have also injected directly supra-clavicular nodes, and other lungs. No positive evidence of radiation necrosis has been observed, but no marked radiation effect on the neoplasm has been found.

They consider the tissue tolerance in dogs to be at least more than 100 mc. Of the 25 mc. dose of active material, that which transmigrated the pulmonary alveolar walls and gained access to the circulation delivered some 2,000β "r" to the liver, 40,000 - 60,000 *e.r.* to the pulmonary parenchyma and 250,000 to the affected nodes. If the volume of the adult human lung is equivalent to 5 times that of a dog, it is questionable if a potential cancericidal dose could be administered in this way.

4. Parenteral Administration for Systemic Effect

Total body irradiation, using bromine, chlorine, sodium or calcium, or other elements generally employed by the major tissues of the body can be a topic for theoretical consideration. But for the useful therapeutic applications of total body irradiation, we have far more facile means in our conventional levels of x-radiation, or by means of special apparatus up to 2 mev, the Cobalt[60] beam unit or a betatron.

However, in the blood dyscrasias, Phosphorus[32] offers some possibilities. The rate of uptake by various organs or systems and of excretion will tend to vary with each individual, so that in some degree dosage cannot be predicted by the book. For intravenous administration, Low-Beer, Lawrence and Stone have developed a method and tables for estimation of the amount retained, assessing it during the first three days after administration as a percentage of the dose given, and subsequently as a percentage of the activity which had been retained as of the third day.

In general, the most active systemic, organic or cellular interest in phosphorus is exhibited by the skeleton, spleen, liver, kidney, muscles, blood, skin and nerve tissue in descending order. Low-Beer, Blais and Scofield observe that 6-24 hours after single or multiple test doses of 4-9 microcuries/kgm in the form of $Na_2HP^{32}0_4$ the concentration in bone is 4-6 times greater than in muscle, etc. Bone, spleen and liver, which represent some 10-12% of the total body weight, are all involved in haemopoiesis, and concentrate or use phosphorus 6-10 times as much as all other tissues.

If, in the average human, these three components of the haemopoietic system have a dose ratio of 34.4/10 compared with one of 35.6/90 for the remaining tissues, we may assume that the major haemopoietic tissues will receive a dose of P^{32} proportionately some nine times that of the rest of the body.

It has been known for a long time that the leukocytic cells of the blood were highly sensitive to irradiation, manifesting decrease in cell division in both normal and leukemic bone marrow.

It is probable that the general systemic effect of the radiation carried by P^{32} will be enhanced by the utilization of that element in the synthesis of ribose nucleic acid for the

cytoplasm and desoxyribonucleic acid of the nucleus, affecting more specifically the cellular reproductive mitotic cycle by carrying the irradiation into the most intimate regions of the haemopoietic cells.

Therefore, it is logical to assume that specific systemic effect in the modification, if not full control or cure of abnormal haemopoiesis should be possible with parenteral administration of radioactive phosphorus.

Osgood and his associates have suggested initial maximum doses of 20 microcuries/kgm. for the lymphocytic leukemias, or 40 microcuries/kgm. for the granulocytic series, with a subsequent dose of 100 microcuries/kgm. in 1-3 weeks, which tend to bring the cases under control in 4-12 weeks (average 6), followed by maintenance doses of 6 microcuries/kgm/month at intervals of 10 weeks (4-12), dependant upon the patient response.

As in total body x-radiation, which many of us have used with appreciable success, it is not probable that the total life span will be materially lengthened, but the comfort of the patient and his ability to carry on a more normal existence are increased.

Some success has also been had in the relief of multiple myeloma with P^{32}. Corrigan has reported to me personally definite improvement of dramatic character in one or two patients, with the oral administration of radiophosphorus. As in leukemia, or in the use of general body x-irradiation, care must be taken to not overtreat. Small initial doses with subsequent auxilliary dosage should be employed.

The major success with parenteral P^{32} therapy for systemic effect has been in the modification of polycythemia vera. We consider that an initial dose of 6 mc. is advisable, to be supplemented, if necessary, in 3 months.

Further development of possible systemic therapeutic agents incorporating radioisotopes will require greater knowledge than we presently have of physiologic chemistry and cell metabolism.

5. Parenteral Administration for Specific, Organic or Cellular Effect

As in the parenteral administration for systemic effect, the use of a radioactive isotope for specific organic or cellular irradiation requires that the active element and the compounds of which it is a part, or to which it may be attached, are peculiarly physiologically useful to the particular organ or cell which is to be affected.

Secondly, neither should be chemically toxic, nor should the active element be one which the body may readily detach or extract as a substitute in shortage of another (as Strontium or Yttrium in replacement of Calcium), transfixing same in the tissues which are not to be irradiated.

Further, it must not have an undesirable radiation quality nor half-life.

The desirable qualities are:

(a) A relatively high degree of selective chemical affinity or use which a specific tissue or cell-type has for the element or its compound, and relative metabolic activity of that tissue or cell group;

(b) A relatively high degree to which the "uptake" (either by adsorption or utilization) will be effected without material deleterious physiologic or chemical effect by the element or its carrier on other cells, tissues or the body as a whole; and

(c) An appreciable extent to which its radiation will affect the local cell or tissue, to the benefit of the intimately neighboring tissue complex, the whole organ or the entire body, with less deleterious effect on the tissue or whole organism than some other therapeutic agent.

The outstanding isotope in this category is radioactive iodine, which satisfies virtually all criteria. The special requirement and use of iodine by the thyroid gland in major contrast to all other tissues, save for the transient metabolism of thyroid hormone in the body and return of the iodine in a non-organic radical, is particularly favourable. The association of disturbed thyroid metabolism with other metabolic and some cardiovascular dysfunctions increases its value as a therapeutic agent.

I^{131} is a singular example for such purpose, with a half-life of 8 days, beta radiation of 0.595 mev which can penetrate some 2.2 mm., and a gamma component of sufficient energy (0.367) to permit very accurate quantitative external detection, and the assay of body-fluid and urine samples in both mass and detail. Its dominant excretion by the urinary tract is valuable in assessment of the clinical physiologic status of the patient.

The indications for therapy with I^{131} are:

(a) Hyperthyroidism in patients over 40-45 years of age;

(b) Hyperthyroidism in younger individuals when anti-thyroid drugs fail and/or surgery is refused;

(c) Hyperthyroidism complicated by/or associated with cardio-vascular disease; or

(d) Recurrence after surgical intervention.

The contra-indications appear to be

(a) Acute hyperthyroidism in younger patients;

(b) Pregnancy, and

(c) Nodular goitre.

In each case, close co-operation and consultation by the internist, surgeon and radiologist should be had in the decision as to the relative advisability of surgical intervention or a test of the antithyroid drugs in preference to I^{131} therapy.

Careful tracer studies (over a 30-36 hour period following ingestion), including assay of the urinary excretion, must be done of each candidate before the decision to treat with I^{131} is finalized. Supplementary and comparative observations on the basal metabolic rate, blood cholesterol and serum protein-bound iodine are important.

The optimum therapeutic dose for *non-malignant thyroid disease* varies from observer to observer. There is also a considerable variation in patient response, of which some estimate will be made from the tracer study. We consider at present that it is better to administer a standard initial dose, and repeat in 3-4 months if required. The proper dosage range is probably between 8,000 and 10,000 rep. Some patients can be brought to a euthyroid state with slightly less than 5,000 rep.

A latent period of 3-4 months should be anticipated before major clinical evidence of the effect of treatment. Anti-thyroid drugs may be required during this interval. The clinical reaction must be observed closely, especially as to remission of symptoms, change in size of the gland, subsidence of tachycardia or other cardiovascular signs, or alteration of the peripheral circulation. Careful re-assessment is necessary before any supplemental dose is given. An hypothyroid state may be induced from which a certain percentage will spontaneously recover in time.

Similar results can be accomplished by the experienced therapist with properly administered conventional x-radiation. The indications are the same. For x-radiation, pregnancy and youth of the patient are not equivalent contra-indications.

In regard to *malignant disease* of the thyroid, since Hamilton's first observation and Seidlin's initial report on treatment with I^{131}, there has been little advance in our knowledge of how to induce active uptake of radioiodine in the majority of carcinomas of the thyroid. Only some 10% are "iodine-metabolizing". Neither withdrawal of iodine from the diet, creating a potential iodine hunger, nor the administration of thyrotropic hormone has much effect. If there are metastases, the removal of the involved thyroid gland surgically may induce greater avidity for iodine in the metastatic deposits. There is some hazard in precipitation of a myxoedematous state by the use of large doses of thiouracil, and then a sudden withdrawal, in preparation for a therapeutic dose of I^{131}.

Dr. Cox and Dr. Stephens-Newsham have been carrying on some studies in an attempt to find a better means of determining the size and weight of the thyroid for estimation of dosage. So far, we have not had much success over the "palpate and guess" method.

At this time, no other radioactive elements or compounds of major usefulness for specific organic effect have been discovered. No additional specific cellular affinity is clearly evident.

Some interesting work is in progress at the Brookhaven laboratories and hospital upon the direct application of neutron radiation to the brain in order to activate boron, which has been given parenterally, in the treatment of glioma. This might be included in the specific organic effect.

So much for what is presently known and moderately well established, at least in clinical research, as to the therapeutic usefulness of radioactive isotopes. It is not possible nor practicable to cover in any one paper all the detailed ramifications or available information.

What then of the future and the further potentialities?

The physicists and physical engineers have already "outrun the pack" in their development of nuclear reactors. Higher neutron fluxes in the new "piles" probably will be able to provide larger quantities and higher specific activity of many of the currently identified isotopes in the near future. The "pack", as represented by biology, biochemistry, physiology, clinical medicine and radiology, have much to do in the investigation of cellular and organic chemistry, and metabolic processes generally, of which so much remains unknown. Extensive studies must be inaugurated and completed in these fields, for which the radioisotopes will be most valuable as "tags" to trace various chemical compounds and their metabolic pathways in and out of the body, its several tissues and specific cells.

It is hoped that for this purpose, at least, clinical physiology will be returned to a proper place in the medical team.

There are probably other items to be discovered as intriguing as in the case of Hafnium[181], an element which I, and probably you have not known well, if at all, even in the stable isotope. It has a half-life of 50 days and a beta radiation of 0.46 mev., with gamma components of 0.5, 0.35 and 0.13. Why it should concentrate, when incorporated in one compound, especially in the zona glomerulosa of the adrenal cortex, is not known. But this may become of real importance if we should require specific radiation in that area. Further, its proportional major deposition in the more common sites of the liver or the spleen can be altered by its incorporation in a citrate, catecol or mandelate. Similar manipulation may be practical with several other radioisotopes to accomplish specific organic effect.

The title of this paper includes consideration of the further potentialities of the radioactive isotopes as therapeutic agents. Perhaps Hafnium[181] or some other presently unappreciated element or compound may be found to be a potent tool in the treatment by internal specific irradiation of certain non-malignant diseases, as well as cancerous tissues.

I do not have the temerity at this stage of our knowledge to attempt to forecast the future further.

We have learned much in these very few recent years. The tools are here to use. But we and our colleagues must think, and must explore new ways to use them in order to do the job.

I envy the younger generations their opportunities.

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AUTOMATIC KILOVOLTAGE CONTROL IN SPOT FILMING*

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The importance of spot filming is readily apparent to anyone making examinations of the gastro-intestinal tract. It might be wise to review the reasons for spot filming as it applies to gastro-intestinal work. It is safe to say that the major number of radiologists rely more on their fluoroscopic observations to find a lesion than they do on the radiographs made in the conventional manner. Certainly, in our opinion, the importance of an adequate fluoroscopic examination cannot be overemphasized. However, having identified the lesion, one then must make the necessary radiographs to:

(1) establish a permanent record of the lesion, and

(2) to adequately study the demonstrated lesion.

For these purposes, the spot filming technique is far superior to conventional radiography. In addition to the study and demonstration of a lesion, it is becoming more and more prevalent to use the spot filming device to make the routine studies of the whole of the stomach using single exposures on 8 x 10 film. With present-day equipment, these films can be of as good quality as those made in the conventional manner, and the necessity of repositioning the patient for the use of the overhead tube and bucky is obviated.

What is considered satisfactory radiography with reference to the gastro-intestinal tract? We believe that if all the films made are of diagnostic quality and the exposure time is short enough to prevent movement of the part, then the method is adequate. In order to obtain films of equal diagnostic quality, one must have some arrangement for altering the factors used in the exposure when the position of the patient is altered. This has been done by changing the time factor which can be controlled automatically with the photo-electric cell. However, in altering the time factor, a point may be reached at which movement may inadvertently occur. Moreover, with the confined scanning presently associated with the photo timing method, not all the films are of diagnostic quality.

The other method of altering exposure factors which might be used is a variation in kilovoltage. This can be done manually either by some device which is fixed to the screen, or by having a person at the controls make the kilovoltage change necessary for the altered position of the patient. If this manual correction of kilovoltage is not resorted to, then the usual procedure used is to choose an average kilovoltage, usually that necessary for the oblique position of the patient, and make all films with this fixed kilovoltage. In most cases, this results in some films being under-exposed and others over-exposed, depending upon how great a variation from the oblique is used during the course of the examination.

Realizing that when kilovoltage is varied manually for the making of spot films all the films can be of good diagnostic quality, it was felt that it would be ideal to have some method which would automatically change the kilovoltage as the position of the patient was altered.

A device was designed which would automatically change the kilovoltage setting in accordance with the thickness of the part being examined leaving the time and milliamperage factors constant. As a measuring device to denote the changes in the thickness of the examining parts, the screen tower acts as a measuring caliper. The screen tower is usually telescopic in its mounting, and a small variac transformer is attached in a suitable container to the rear of the screen tower. This variac is operated by means of a rack and pinion gear, so that the movement of the screen to and from the table rotates the small variac.

This small variac which is attached to the screen tower operates a modulating type motor which is located at the X-ray control. This modulating type motor is reversible in action and the shaft of this motor is attached by gears to a heavy variac transformer. This heavy variac transformer is connected across

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certain points of the X-ray auto-transformer which are in use during this particular technique.

It can be seen then that the movement of the screen towards the table can be made to automatically operate the motor and the variac in one direction. When the screen is raised or moved further from the table, the motor will tend to run in the opposite direction. By proper voltage connections and prearranged calibrations of the controlling variac on the screen tower with the reversible motor in the X-ray control, it is possible to have the motor shaft follow the excursion of the screen at all times. The large variac which is connected with the motor and to the auto-transformer of the X-ray machine across certain fixed points can then increase or decrease the kilovoltage at the time of spot filming.

The existing unit has a dual range kilovoltage selection. The upper range is between 70 and 100 kilovoltage and the lower range for use in the examination of the upper parts of the oesophagus has a range of 50 to 80 kilovoltage. Either range can be immediately introduced by a toggle switch. The device has been used with the fixed milliamperage of 200 and all of the examinations done have been possible between the time settings of 1 10 to 3 10 second; the time setting being determined when the patient first is seen. The times used were with a fixed grid in position during the spot filming.

With this automatic device installed, films were then made in all positions which one might deem necessary during a gastro-intestinal examination. The time and milliamperage were, of course, constant, the only variable being the kilovoltage which varied automatically with the position of the screen. The device has been in use for four months, and approximately 400 cases have been done using the method. These cases represented a full cross-section of the patients referred through the outdoor and the wards of a general hospital.

The examinations included upper gastro-intestinal tract, colon, and spot films of the bronchial tree, the latter being made at exposure times of 1/30 second, fixed grid in position. The results of the examinations indicated that the films made using this automatic kilovoltage control were all of good diagnostic quality. When exposures were made to show the mucosal relief pattern or air — barium contrast studies of the pyloric antrum or fundus, the quality of the film was similar to that obtained when the stomach was completely filled with barium, and the exposure made over a completely dense area. It was found, moreover, that the introduction of the pressure cone caused an increase in kilovoltage sufficient to compensate for the reduction in field size coincidental with its use.

Summary:

A method of improving the quality and facilitating the making of spot films by automatic kilovoltage control has been described. The device used consists of a measuring caliper which is fixed to the screen tower and by virtue of its position has effect upon a variable transformer through an electric circuit. The method has been applied so far only to spot filming of the gastro-intestinal tract and bronchial tree. The method overcomes the problems of:

(1) increased time of exposure, and

(2) inconsistency of exposure due to confined scanning, both of which are associated with the photo-timing method. The device has been in continuous use without service since its installation four months ago, and no change in the existing timer or screen tower was necessary for the installation.

HEMANGIO-ENDOTHELIO-SARCOMA OF BONE*

with

A CASE REPORT

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The infrequent occurrence of primary malignant vascular neoplasms of bone is reflected in the paucity of cases reported in the literature, — the present inclusive proven number being about twenty-five. Just so has this numerical limitation retarded our agreement on a completely acceptable terminology and made for confusion as to histogenesis and classification.

Important recent studies of those cases having satisfactory criteria, have clarified their pattern very considerably, and have particularly orientated the pathogenesis. Early differences of opinion were aggravated by the incorrect inclusion of highly vascular tumours which were not tumours of vascular origin. The exhaustive and excellent works of Thomas[1] and Stout[2] have greatly augmented our knowledge of the subject. Some early authors as MacCullum[3] were loathe to agree that there was such a tumour of distinct endothelial origin. Many others differed as to what should be included in the term endothelium. Maximow and Bloom[4] maintained that this term should apply only to the single layer of cells which line the inner surfaces of the blood and lymph vessels and the heart. Pathologists of to-day appear in agreement on this and also on the principle that a tumour of this origin must show vasoformative characteristics.

Ewing's[5] classification of bone tumours, as accepted by the Registry of the American College of Surgeons, divides angioma into benign and malignant. Benign are further divided into cavernous angioma and plexiform angioma (X-ray appearance). The malignant are classified into angio-endothelioma and diffuse endothelioma (Ewing's tumour).

Thomas[1] has made a very significant and excellent contribution by further dividing some 15 known malignant angiomas of the Bone Sarcoma Registry, American College of Surgeons, into two classes — angio-endothelioma and angio-sarcoma. Kolodny[6] indicated the reasons why angio-endothelioma of bone is a distinct clinical entity and warned of the possibility of confusion with certain tumours of metastatic origin. Freilich and Coe[7] emphasize that the descriptive term of angiosarcoma should be reserved for cellular malignant angiomas which have a definite vasoformative tendency.

Discussion

At one end of the angiomatous scale there is the well differentiated, highly developed blood vessel type, the slow-growing benign angioma. At the other extreme is the rapidly growing, poorly differentiated, cellular angioblastic tissue, the angio-sarcoma, having cells of divergent morphology, with mitoses, metastases, and invasion of adjacent tissues.

Like two other cases in the literature, the present one to be reported was significant for the very extensive involvement of the pelvic bones. Gordon Gordon-Taylor[8] describes a hind quarter amputation for a pulsating tumour of the innominate bone. Histological studies indicated a moderate degree of differentiation with evidence of a moderate degree of malignancy. Hauser and Constant[9], detail the progressive extension of the disease in a patient on whom they have a nine-year follow-up. The gradual and nearly complete invalidism of the patient is detailed. The first abnormal changes were noted in the upper section of one femur. A little later, a similar appearance was noted in the opposite one. Shortly thereafter the pelvic bones were invaded. Final X-rays show involvement of almost the entire pelvis. Obviously, when the disease is so extensive, surgery is impracticable. The authors state that treatment with X-ray and Radium failed to check the local spread. This observation is at variance with the response to radiation of the case here reported; nevertheless, when possible, surgical extirpation appears to be the treatment of choice. Of twenty-three cases of hemangio-endothelio-sarcomata in the literature, nine received some form of surgical treatment.

Prognosis

The insidious and inevitable crippling, and death which faces these patients, is borne out by published statistics. The longest known survival was listed by Thomas[1], the patient being alive ten years after surgery. Kolodny[6] refers to one who died four years after an amputation. Pritchard[10] reported a case of hemangio-endothelioma of the wrist bones

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who was living three years after amputation. Deep X-ray therapy was reported not to have retarded the tumour spread, but only 800 "r" was given. The extremely malignant nature of some of these tumours is well illustrated in a case reported by Warner and Singleton[11]. Their patient died about six months after the first symptom of local pain in the right hip area. Post-mortem examination indicated an extensive primary involvement of the right femur with secondaries in the lungs, liver and pleura.

Diagnosis

Local pain and swelling are the common complaints which awaken the patient's first concern. Physical examination is of little help. X-ray examination is greatly contributory, as vascular neoplasms have a significant, striated, lacelike appearance. It remains, however, for histological studies after biopsy to decide the true type, and by this, and the presence or absence of metastases, to prognosticate the future course. Special silver reticulin staining is sometimes an aid, states Stout[2]. This differentiates the vascular tubes, and brings out the distinctive pattern when cellular overgrowth obliterates it with other stains. Thus, the exact cellular location, whether endothelial or pericytic can be decided. Even histologically, the similarly of some secondary malignancies may offer confusion: particularly to be mentioned is secondary hypernephroma. Stout's[2] histological requisites for angiosarcoma are:

(a) Formation of a typical and excessive endothelial cells;

and

(b) Formation of vascular tubes in a delicate framework of reticulin fibres and a marked tendency to luminal anastomases.

To add to the recording of this rare condition, the present case is reported and attention is drawn to the favourable response to deep X-ray Therapy. In view of the histological report it appears that this tumour should be placed in the small subdivision of angio-sarcoma.

The patient, a 52-year-old male dining car steward, came to us in March, 1950. There had been continuous low-back pain for six months, principally noticeable with the vibrating of the train. He experienced no pain in walking, sitting or lying down. He was not incapacitated in any way and he continued to work; nor had the character or severity of his symptom changed in the intervening six months.

General physical, neurological and laboratory examinations were negative; there was no complaint of pain with movement or with local manual pressure. There was no local swelling.

X-ray examination (Figure 1A) was made solely because of the low back pain and it revealed an extensive destruction of the left iliac bone; the X-ray diagnosis was hemangioma of bone. Biopsy was performed and the surgeon reported that almost the entire wing of the ilium was involved. The tumour was soft and friable and the iliac bone was a sort of shell; in some places the tumour had broken through and invaded the adjacent muscles.

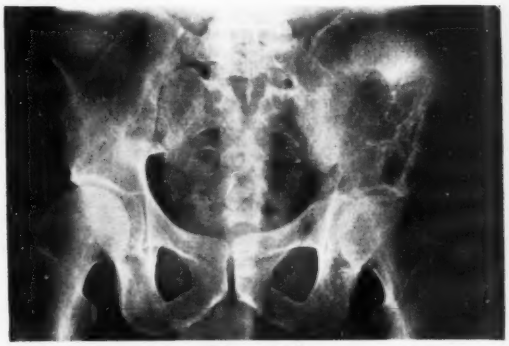

Figure 1A
Extensive destruction of the left iliac bone and probable slight destruction of the right iliac bone. March 11, 1950

The pathological report stated that the examined tissue was composed of irregular strands and cords of malignant cells (Figure 3). There was a great deal of variation in the size, shape and staining characteristics of the malignant cells. Some showed large, pale, vacuolated nuclei with well marked nucleoli. Collections of chromatin were seen to be situated at the periphery of the nuclei of these malignant cells, leaving the central portion of many of them clear and translucent. Also seen amongst these were a great many cells whose nuclei were dark, irregular in outline, with considerable variation in size and outline some showing mitotic figures. Many giant cells of a typical character were seen. One characteristic of this tumour is its attempt to form small sinusoidal spaces. Many of these were filled by proliferating tumour cells, but some appeared to be filled by red blood cells.

Pathological Diagnosis — Angio-sarcoma of left iliac bone.

Treatment

In view of the extent and location of the disease, surgery was contra-indicated and deep X-ray therapy was instituted. A tumour dose of 2157 "r" was given in a 14-day period. Physical factors were 250 Kv-15 ma. Thoraeus #3 filter, H.V.L. 3 Cu., anterior and posterior ports 15 x 20 cms. Following X-ray films three months later, indicated local recalcification in the ilium. Using the same factors, a further tumour dose of 2157 "r" was delivered.

In August 1950, similar radiographic changes were observed in the right iliac bone. (Figure 1B) A tumour dose of 2520 "r" was given via anterior and posterior ports. In January, 1951, a further 1005 "r" (tumour dose) was administered to the left ilium through a lateral 15 x 20 port, and in February, 1951, an additional 1440 "r" was given to the right iliac region.

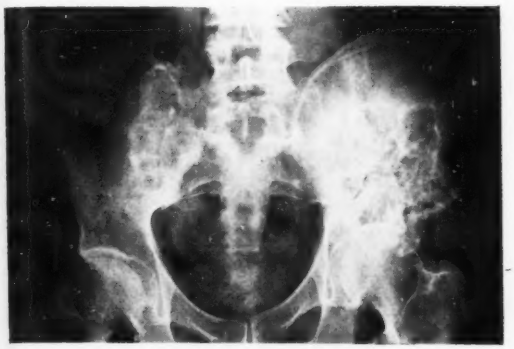

Figure 1B

Recalcification in the left ilium and extensive bone destruction of the right ilium. August 30, 1950.

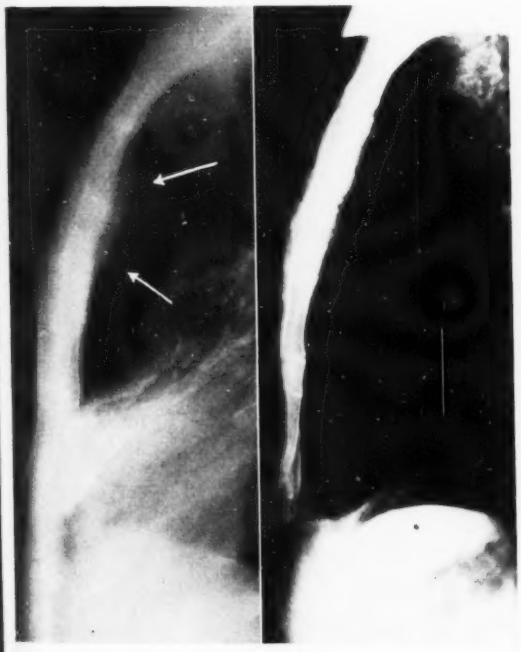

Figure 2A

Destruction of sternum with retro-sternal mass. July 1952

Figure 2B

Extensive destruction of body of sternum. October 1952

In July, 1952, two and one-half years after onset of symptoms in the left ilium, a tender mass appeared over the upper sternum. X-rays revealed destruction of the corpus manubrii with a soft tissue mass retrosternally (Figure 2A). This was considered to be a metastatic lesion which was confirmed by biopsy. A tumour dose of 2300 "r" was given through a 10 x 15 cm anterior port. The visible mass anterior to the sternum disappeared in about two months and X-rays revealed the disappearance of the retro-sternal mass and recalcification of the sternal body (Figure 2B).

After the initial treatment period of March 1950, the patient returned to work and except for time off for further treatment, he continued to work. The pain in the left iliac bone disappeared in about one month and has not returned.

In September, 1953, the patient experienced slight pain in the right sacro-iliac area and X-ray examination suggested some probable revival of activity (Figure 1C). A tumour dose of 1070 "r" was administrated. Thus there

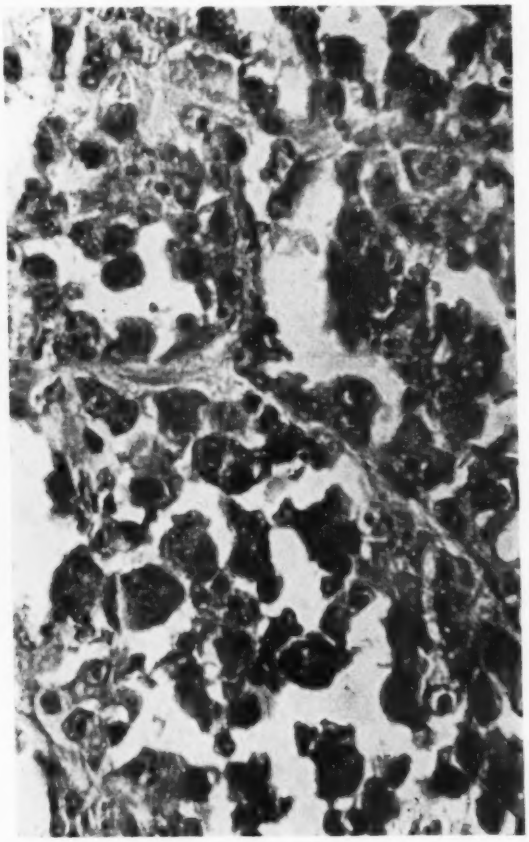

Figure 3

High power demonstrating malignant cellular change.

has been a tumour dose of 5319 "r" delivered on the left pelvis and 5230 "r" on the right side. There is slight skin telengectasia posteriorly on each side.

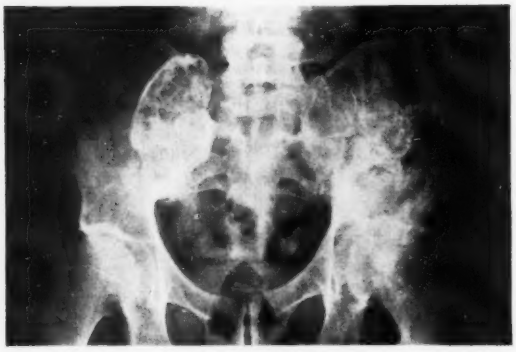

Figure 1C
Generalized recalcification of the left ilium. Possible further activity in right iliac bone.
September 1, 1953

Review of the X-ray films reveals that recalcification commenced a few weeks after the initial treatments, and the local spread and apparent activity of the disease in all three affected areas has been controlled. Recent X-rays of the rest of the skeleton, skull and chest are negative.

It would seem that without X-ray therapy the patient would have become an invalid long ago, whereas he has continued quite happily at work.

At the present time, he experiences no pain, loss of strength, or other symptoms, feels quite normal and carries on his regular occupation.

Summary

A case of angio-sarcoma is reported. Attention is drawn to the excellent reaction to deep X-ray therapy. It appears that a moderately high tumour dose may be rewarded by a good temporary, if not permanent recovery.

BIBLIOGRAPHY

1. Thomas, Atha, Surg. Gyn. and Obst., 1942, Vol. 74, pages 777.

2. Stout, Arthur Purdy, Annals of Surgery, 1943, Vol. 118, No. 3, Page 445.

3. MacCallum, W.G., Text Book of Pathology, 6th Ed., Page 1055, Philadelphia, W.B. Saunders Co., 1938.

4. Maxinow, A., and Bloom, W., Text Book of Histology, 3rd Ed., Philadelphia, W. B. Saunders Co., 1938.

5. Ewing, J., Neoplastic Diseases, 4th Ed., Philadelphia, W. B. Saunders Co., 1940.

6. Kolodny, A., Angio-Endothelioma of Bone. Arch. Surg. 12 — Pages 854-866, 1926.

7. Freilich, E.B., and Coe, G.C., Amer. Journal Cancer, 1936, 26:269.

8. Gordon-Taylor, Gordon, Journal of Bone and Joint Surgery, Vol. 31-B, Page 410: 1949.

9. Hauser, Emil D. W., and Constant, George A. Journal of Bone and Joint Surgery, Vol. 30-A No. 2.517-521, April 1948.

10. Pritchard, J. E., Hemangio-Endothelioma of Bones of the Wrist. Can. Med. Assoc. Journal 24.689-692. 1931.

11. Warner, W.P. and Singleton, A.C., Angio-Endothelioma of Bone with Pneumo-Thorax due to Pleural Metastases, Can. Med. Assoc. Journal 29: 610-612, 1933.

MEETINGS

Special General Meeting — June 1954

A Special General Meeting of the Canadian Association of Radiologists will be held in the Board Room of the Academy of Medicine Building, 1807 W. 10th Avenue, Vancouver, on Tuesday, June 15th, 1954, all day.

Fifth Inter-American Congress of Radiology

The Fifth Inter-American Congress of Radiology will be held in Washington, D.C., April 24th-29th, 1955.

Enquiries concerning the Congress should be sent to: Dr. Philip J. Hodes, 3400 Spruce Street, Philadelphia 4, Pa.

Fourth Symposium Neuroradiologicum

The Fourth Symposium Neuroradiologicum will be held in London, England, September 13th-17th, 1955.

All wishing to contribute papers are invited to communicate as soon as possible with the Honorary Secretary, Dr. R. D. Hoare, at the National Hospital, Queen Square, London, W. C. I.